From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

ÉRKEZETT

PCT DANUBIA
Szabadalmi és Védjegy Iroda Kft.

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90714/S
2002.01.21.P92928
5877-A PT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

	Date of mailing *(month/year)* 15.01.2002
Applicant's or agent's file reference 92928-352-PT/tm	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/HU00/00099	22/09/2000	23/09/1999

Applicant
GYOGYSZERKUTATO INTEZET KFT. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
92928-352-PT/tm		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/HU00/00099	22/09/2000	23/09/1999

International Patent Classification (IPC) or national classification and IPC
C07D307/88

Applicant
GYOGYSZERKUTATO INTEZET KFT. et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22/03/2001	15.01.2002

Name and mailing address of the international preliminary examining authority:

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/HU00/00099

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-23 as originally filed

Claims, No.:

1-5 as originally filed

Drawings, sheets:

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☒ the claims, Nos.: 3,4

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,2,5
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1,2,5
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1,2,5
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: JONES, DERRICK FLEET ET AL: 'Preparation and antitumor properties of analogs and derivatives of mycophenolic acid' J. MED. CHEM. (1971), 14(4), 305-11 , XP002165088

D2: SUZUKI, SEIKICHI ET AL: 'Antitumor activity of derivatives of mycophenolic acid' J. ANTIBIOT. (1976), 29(3), 275-85 , XP000067668

D3: JONES, DERRICK FLEET ET AL: 'Microbial modification of mycophenolic acid' J. CHEM. SOC., C (1970), (12), 1725-37 , XP002165092 cited in the application

2.1 Novelty (Article 33(2) PCT)

2.1.1 Claim 1 of the present application pertains to a microbiological process for the preparation of mycophenolic acid and amide derivatives comprising carbon and nitrogen containing sources and a *Penicillium waksmani* fungal strain being capable of producing mycophenolic acid derivatives. The process of present claim 1 is novel with respect to e.g. D1, where a compound falling under formula I of claim 1 is disclosed (cf. page 306, col. 1, compound 33), and mycophenolic acid itself is mentioned (cf. page 305, compound 1). According to D1, the mycophenolic acid derivative compound 33 (falling under formula I of the present application) is prepared by chemical synthesis starting from O-acetylmycophenolic acid (cf. page 309, col. 2). According to D2 mycophenolic acid is isolated from a broth of *Penicillium* (cf. page 275, first three lines). The derivatives of D2 are all obtained by synthetic chemical modification of mycophenolic acid.

2.1.2 D3 discloses a microbial modification of mycophenolic acid to obtain derivatives thereof, but it does not disclose preparing of mycophenolic acid, derivatives thereof and derivatives of amides thereof starting from a culture medium containing C and N sources. D3, however, discloses a compound which is structurally closely related

to the compound of claim 5, i.e. a compound according to formula I of claim 1 where R^2 represents hydroxy and R^1 is hydroxymethyl (cf. p. 1728, col. 1, compound 12). This compound 12 of D3 is a fermentation product of mycophenolic acid by using e.g. *Aspergillus carbonarius* or *Penicillium daleae*. The corresponding amide, which is the subject-matter of claim 5 of the present application, is not disclosed in the prior art.

2.1.3 Consequently, the novel features of claim 1 consist in the use of a novel fungal strain of *Penicillium waksmani* and the subsequent bioconversion of the mycophenolic acid and acid derivatives with *Streptomyces* microorganisms to yield the corresponding amides. The subject-matter of claims 1,2 and 5 is therefore novel in the sense of Article 33(2) PCT. Claims 3 and 4 have been deleted by the applicant in his letter of 05.09.2001.

2.2 Inventive Step (Article 33(3) PCT)

2.2.1 The document D3 is regarded as being the closest prior art to the subject-matter of claims 1 and 5, and shows the preparation of mycophenolic acid derivatives starting from mycophenolic acid by using various microorganisms (cf. section 2.1 above). The subject-matter of claim 1 therefore differs from this known methods for producing mycophenolic acid and its derivatives in that an novel fungal strain capable of biosynthesising mycophenolic acid is used, and that previously not disclosed *Streptomyces* microorganisms are subsequently used to obtain amide derivatives of mycophenolic acid.

2.2.2 The technical problem to be solved by the present invention may therefore be regarded as to provide a further method for the preparation of mycophenolic acid and it amide derivatives thereof.

2.2.3 The solution to this problem proposed in claim 1 of the present application is considered as involving an inventive step (Article 33(3) PCT), because the use of a previously not known fungal strain to produce mycophenolic acid is not suggested anywhere in the available prior art.

2.2.4 The novel compound of claim 5 is directly available by the novel and inventive process of claim 1. The technical problem to be solved by this novel mycophenolic acid derivative is to provide another immunosuppressive and antitumor compound. The inventive step of this compound can be seen in the fact that it is obtained in an inventive process of claim 1 and that a person skilled in the art would not have expected it to be a further solution of this technical problem underlying the present invention. A person skilled in the art would expect that mycophenolic acid derivatives not having a carboxyl group, would loose e.g. their antitumor activities, because it is the teaching of D1, that the carboxyl group of mycophenolic acid is **important** for high antimitotic activity, and correspondingly for the antitumor properties of the compounds. Hence, it is to be regarded as an unexpected effect of the compound of claim 5 to be useful as antitumor or immunosuppressive compound.
Consequently, claim 5 is also inventive in the sense of Article 33(3) PCT.

2.3 Industrial Applicability (Article 33(4) PCT)

The process and the novel compound of the present application can be used to provide medicaments containing mycophenolic acid and derivatives thereof.